Minutes of a teleconference

Date:	February 12, 2002
Application:	NDA 20-386 COZAAR (losartan potassium)
Sponsor:	Merck and Company, Inc.
Subject:	Advisory Committee Discussion
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Sandra Birdsong

FDA Attendees

Robert Temple, M.D., Director, Office of New Drug Evaluation 1, HFD-101
Raymond Lipicky, M.D., Director, Division of Cardio-Renal Drug Products (HFD-110)
Douglas C. Throckmorton, M.D., Deputy Director, HFD-110
Natalia Morgenstern, Chief, Project Management Staff, HFD-110
Sandra Birdsong, Regulatory Health Project Manager, HFD-110

Merck Attendees

Bonnie Goldmann, M.D.
Michael Elia, Ph.D.
Michelle Kloss

Background

This meeting is a follow-up to the teleconference held on February 1, 2002 regarding cross-referencing Type II diabetes data between Merck and Bristol-Myers Squibb (BMS).

Meeting

Merck was not enthusiastic about letters giving BMS the right to reference the losartan database, and giving Merck the right to reference the irbesartan database. Merck's Concern is that it would be perceived that two pharmaceutical companies are somehow working together, and were worried about the impact of such letters on the evidentiary standard.

The firm suggested that BMS could do a presentation at the Advisory Committee along with Merck. Merck also believes that it would be possible for the Advisory Committee to consider the data from irbesartan that was discussed at the last Advisory Committee without the two sponsors giving right to reference.

The sponsor stated they would be willing to discuss this internally, but they are not optimistic about giving permission to cross-reference.

Conclusions

- Merck will discuss the issue of cross-referencing internally
- Dr. Temple will

Sandra Birdsong
Meeting Recorder

Robert Temple, M.D.
Concurrence, Chair

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/s/

Sandra Birdsong
3/12/02 04:46:39 PM

423-989-8055DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

Woodmont II
1451 Rockville Pike
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DEPARTMENT OF HEALTH & HUMAN

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5600 Fishers Lane
Rockville, MD 20857

Transmitted to FAX Number: 484-344-2516

Attention: Michael Elia, Ph.D.

Company Name: Merck and Company, Inc.

Phone: 484-344-3180

Subject: Teleconference Minutes

Date: March 12, 2002

Number of pages including this cover sheet: 3

From: Sandy Birdsong
Phone: 301-594-5334
FAX: 301-594-5494

Dear Dr. Elia:
The minutes of our February 12, 2002 teleconference accompany this cover sheet. You are responsible for notifying us of any inconsistencies in your understanding of the content of the meeting. Thank you.
Sandy

MESSAGE CONFIRMATION

03/12/02 17:36
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Transmitted to FAX Number: 484-344-2516

Attention: Michael Elia, Ph.D.

Company Name: Merck and Company, Inc.

Phone: 484-344-3180

Subject: Teleconference Minutes

Date: March 12, 2002

Minutes of a Teleconference

Date:	February 1, 2002
Application:	NDA 20-386 COZAAR (losartan potassium)
Sponsor:	Merck and Company, Inc.
Subject:	Losartan for Diabetic Nephropathy
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Sandra Birdsong

FDA Participants

Robert Temple, M.D., Director, Office of New Drug Evaluation 1, HFD-101
Raymond Lipicky, M.D., Director, Division of Cardio-Renal Drug Products (HFD-110)
Douglas C. Throckmorton, M.D., Deputy Director, HFD-110
Norman Stockbridge, M.D., Ph.D., Medical Team Leader, HFD-110
Juan Carlos Pelayo, M.D., Medical Officer, HFD-110
Zelda McDonald, Regulatory Project Manager, HFD-110
Edward Fromm, Regulatory Project Manager, HFD-110
Sandra Birdsong, Regulatory Project Manager, HFD-110

Merck Participants

Dr. David Blois, Regulatory Affairs
Dr. Michael Elia, Regulatory Affairs
Ms. Betsy Fallen, Regulatory Affairs
Dr. Michelle Kloss, Regulatory Affairs
Dr. Shahnaz Shahinfar, Clinical Research
Mr. Roger Simpson, Clinical Research
Dr. Stephen Snapinn, Biostatistics

Background

Cozaar® (losartan potassium) was approved for the treatment of hypertension on April 14, 1995. Efficacy Supplement 028 was submitted on December 21, 2001 for treatment of type 2 diabetic nephropathy and the reduction of proteinuria, loosely based on the results of the RENAAL study. The application was given priority review status. The purpose of the teleconference was to ask Merck about sharing their type II diabetes data.

Meeting

Dr. Temple asked the sponsor about their plans to work with Bristol-Myers-Squibb (BMS) regarding the efficacy of their respective products in Type 2 Diabetes. He noted the irbesartan data had been recently reviewed at a Cardio-Renal Advisory Committee, and that the Committee had recommended against approval (the vote was close, however). While the full review of the RENAAL data has not been completed, the published material suggests that the case for losartan 's approval is no more robust than for irbesartan, and that a similar outcome was quite possible when losartan was presented to the Advisory Committee. For irbesartan, the Advisory Committee expressed interest in examining the results from another study with a related drug (such as losartan) as possible additional support for efficacy. The Agency understood that Merck and BMS had talked about the possibility of sharing the data from their respective trials, potentially bolstering their respective cases for efficacy in Type 2 Diabetes. Using efficacy data from one drug to support efficacy of another, related drug is quite unusual and the opinion of the Advisory Committtee would certainly be sought.

Merck said that BMS had initiated contact with Merck, but no decision had been made. In this teleconference Merck discussed the possibility of the two firms providing letters of cross-reference to each other. Dr. Temple stated that the Agency is not urging this as that would be a decision entirely left to the companies, but was seeking to learn about any plans as they could affect our review.

The next Advisory Committee is currently scheduled for April 12, 2002, when the results of the RENAAL study will be discussed, so if the two sponsors want to pursue this avenue there is a tight time frame to work within. Bristol-Myers Squibb (BMS) would need the ability to refer to Merck's RENAAL study and Merck would need to refer to BMS's IDNT study. Both applications would then be discussed at the Advisory Committee in April. The Agency does not see any utility in a combined analysis of the results from the trials.

Conclusions

- The Division plans to discuss the results of the RENAAL trial at the next Advisory Committee. Any discussion of other trial data, such as the data from the irbesartan trials, will require some agreement between the two sponsors allowing the Agency to discuss both.

- Merck will discuss the possibility of a mutual cross-referencing agreement between the two applications and provide their answer to the Agency early in the week of February 4, 2001.

/S/
Sandra Birdsong
Meeting Recorder

/S/
Robert Temple, M.D.
Concurrence, Meeting Chair

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/s/

Sandra Birdsong
2/15/02 10:42:37 AM

Minutes of a Meeting

Application:	NDA 20-386 COZAAR (losartan potassium)
Sponsor:	Merck and Company, Inc.
Date:	April 2, 2002
Subject:	Discuss presentation for April 12, 2002 Advisory Committee
Meeting Chair:	Douglas C. Throckmorton, M.D
Meeting Recorder:	Sandra Birdsong

FDA Participants

Douglas C. Throckmorton, M.D., Acting Director, Cardio-Renal Drug Products Division, HFD-110
Norman Stockbridge, M.D., Ph.D., Medical Team Leader, HFD-110
Juan Carlos Pelayo, M.D., Medical Reviewer, HFD-110
James Hung, Ph.D., Statistician, Division of Biometrics I, HFD-710
Denise Hinton, Regulatory Project Manager, HFD-110
Sandra Birsong, Regulatory Project Manager, HFD-110

Merck Participants

Dr. Bonnie Goldmann, Senior Vice President, Regulatory Affairs
Dr. Michael Elia, Director, Regulatory Affairs
Dr. Michelle Kloss, Senior Director, Regulatory Affairs
Dr. Douglas Greene, Executive Vice President, Clinical Sciences and Product Development
Dr. William Keane, Vice President, Clinical Development
Dr. Shahnaz Shahinfar, Senior Director, Clinical Research
Dr. Jonathan Fox, Director, Clinical Research
Dr. Ray Bain, Vice President, Biostatistics
Dr. Steven Snapinn, Senior Director, Biostatistics
Ms. Betsy Fallen, Associate Manager, Regulatory Affairs

Background

COZAAR (losartan potassium) was approved for the treatment of hypertension on April 14, 1995. This efficacy supplement for the treatment of patients with diabetic nephropathy and the reduction of proteinuria was submitted on November 9, 2002 and given a priority review status. The PDUFA action date is May 9, 2002.

Dr. Throckmorton gave the following background for the April 1, 2002 Regulatory Briefing:

> Two trials (IDNT and RENAAL) of drugs with similar pharmacological activity (irbesartan and losartan, both Angiotensin II Receptor Blockers, ARBs) have recently been submitted to the Agency in support of claims for the treatment of patients with diabetes and nephropathy. The trial using irbesartan (the IDNT trial) was discussed at the January 2002 Advisory Committee and the Committee recommended against approval, as they viewed the IDNT data as less than sufficient. The Committee expressed interest in looking at other available data supporting the efficacy of this class of drugs in diabetic nephropathy, however.
>
> The Cardio-Renal Division will discuss the losartan RENAAL trial results with the Advisory Committee on April 12, 2002. The sponsors for irbesartan and losartan have submitted letters of "right to reference" to allow their respective trials to be considered by the committee as potentially supportive of efficacy for both irbesartan and losartan, and for the FDA to consider the data from both trials in support of their respective claims.

Merck requested this meeting in order to discuss the presentation of losartan at the April 12, 2002 Advisory Committee.

Meeting

Merck stated their purpose for the meeting is to determine the following items in final preparation of the presentation for the Advisory Committee:

1) How is the FDA presentation going to be conducted?
2) Will any cross-referencing be done?
3) The sponsor would like to go through their March 29, 2002 letter that refers to the FDA Advisory Committee Background Package and discuss their list of questions.

Question 1: the FDA Advisory Committee Presentation

Dr. Throckmorton said the Division would not make a formal presentation. The Division will have overheads of the primary endpoints for RENAAL and IDNT. It is possible that sufficient discussion will occur regarding the evidence document that Dr. Throckmorton or Dr. Temple may make a few remarks on it. Merck said they hoped the presentation would focus on losartan, with the understanding that the Advisory Committee will probably ask how the RENAAL study relates to the IDNT study. Merck anticipates that a re-discussion of the irbesartan trials would be avoided, although they understand the Agency does not commonly try to limit discussion by the Committee. The sponsor noted that they had seen the Advisory Committee's draft questions, which are similar, except for blood pressure (BP), to those for irbesartan.

Question 2: Cross Referencing

Dr. Goldmann asked if there would be any comment about right of reference and Dr. Throckmorton replied that there would be if a specific question were asked. Merck prefers that any reference to IDNT be that it is confirmatory of the RENAAL trial results, and that there would be no pooled analyses. The sponsor asked about the membership of the Advisory Committee, i.e., who would be the lead reviewer and whether there would be any external constituents. Dr. Throckmorton replied that the lead reviewer would be the same person who was lead for the irbesartan Advisory Committee, and the two external constituents were also on that Advisory Committee. Dr. Throckmorton informed the sponsor that the Division had sought guidance regarding issues around this unusual format for the Advisory Committee in a regulatory briefing with CDER representatives.

The sponsor asked if Dr. Throckmorton would like a copy of their slides and he responded that he will need only the slides on the life table. The sponsor will provide those slides to the Division later this week.

Discussion of Merck's March 29, 2002 Correspondence:

Dr. Throckmorton stated that some of Merck's comments in their March 29, 2002 letter address parts of reviews that were interpretive and that he would limit the discussion today to the issues related to the data. Both reviewers (Drs. Pelayo and Hung) have reviewed the comments and questions and taken them under consideration
Dr. Pelayo stated he reviewed the sponsor's concerns about his review in their letter, and he acknowledged that he misrepresented the study results when he indicated that the subgroup analysis was retrospective in nature. He stated he had intended to say that the analysis lacked statistical power, and he has corrected pages 5, 7, and 24 of his review accordingly.

Dr. Hung said he removed the *p* Values of the components in the decomposition of the primary endpoint from Table 1 of the statistical review, after he reviewed the concerns stated in their letter. He has filed an addendum to address this issue.

Dr. Throckmorton asked the sponsor what happened to patients after they experienced a doubling of creatinine. Merck replied that patients continued to take study drug until they developed ESRD, started dialysis or until they died.

The sponsor expressed their concern that the Advisory Committee understand the two distinct ways in which the individual components of the primary endpoint are examined by the Agency. Dr. Throckmorton stated that these analyses were standard parts of reviews for trials that included composite endpoints such as RENAAL, and the Advisory Committee will be able to understand these differences. He agreed that if there were questions, as needed, the sponsor should be able to explain those differences easily with a short discussion. Dr. Pelayo noted that changes in the time to doubling of serum creatinine are interpreted as reflecting the same clinical effect as time to ESRD by the

Division. The sponsor referred further to the medical review, but Dr. Throckmorton stated that the items referred to represent our interpretation of the data, rather than the actual data.

Merck also expressed concern that the Advisory Committee might interpret the similar results of RENAAL and IDNT as a drug class effect. Dr. Throckmorton suggested that the sponsor could raise the issue of the difficulty in showing pharmacologically similar agents without talking about class effects.

Merck outlined their Advisory Committee presentation format and asked if they would be permitted to go through the presentation without a large amount of interruptions. Dr. Throckmorton said it would be hard for us to try to limit questions during the presentation; standard advice is for the sponsor to minimize the number of people presenting, and the overall presentation time. Then, as additional issues are brought up in the discussion, the sponsor can be ready with additional details.

Conclusions

Merck stated they would submit their slides within the next few days.

/S/
Meeting Recorder

/S/ 4.10.02
Concurrence, Meeting Chair

RD: 4/4/02/SB

Pelayo/4/5/02
Hung/4/8/02
Stockbridge/4/5/02
Throckmorton/4/5/02

Final: 4/8/02/SB

423-989-8055DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Rockville, MD 20852

Transmitted to FAX Number:	484-344-2516
Attention:	Michael Elia, Ph.D.
Company Name:	Merck and Company, Inc.
Phone:	484-344-3180
Subject:	April 2, 2002 Meeting Minutes
Date:	April 10, 2002
Number of pages including this cover sheet:	4
From:	Sandy Birdsong
Phone:	301-594-5334
FAX:	301-594-5494

Dear Dr. Elia:

The minutes for our April 2, 2002 meeting accompany this fax. You are responsible for notifying us of any differences perceived in meeting outcomes. Please let me know you received this fax. Thank you.

Sandy

MESSAGE CONFIRMATION

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Company Name: Merck and Company, Inc.

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Subject: April 2, 2002 Meeting Minutes

Date: April 10, 2002

Number of pages including this cover sheet: 4

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/s/

Sandra Birdsong
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Rockville, MD 20852

Transmitted to FAX Number:	484-344-2516
Attention:	Dr. Michael Elia
Company Name:	Merck and Company, Inc.
Phone:	484-344-3180
Subject:	Meeting Confirmation
Date:	March 29, 2002
Pages including this sheet:	1
From:	Sandy Birdsong
Phone:	301-594-5334
Fax:	301-594-5494

NOTICE OF MEETING

Application:	NDA 20-386 COZAAR (losartan potassium)
Sponsor:	Merck and Company, Inc.
Date of Meeting:	April 2, 2002
Location:	Food and Drug Administration Center for Drug Evaluation and Research Division of Cardio-Renal Drug Products Woodmont II Office Complex 1451 Rockville Pike Fifth Floor, Conference Room "F" Rockville, MD
Time:	11:00 a.m. – 12:00 p.m.
Purpose:	To discuss April 12, 2002 Cardio-Renal Advisory Committee
FDA Participants:	Douglas C. Throckmorton, M.D., Acting Director, Cardio-Renal Drug Products Division, HFD-110 Norman Stockbridge, M.D., Ph.D., Medical Team Leader, HFD-110 Juan Carlos Pelayo, M.D., Medical Reviewer, HFD-110

Note:

When you arrive at the Security Desk at the Woodmont II building, please have Security telephone our main number, 301-594-5300, to announce your arrival. Also, please be prepared for a routine security inspection upon arrival.

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/s/

Sandra Birdsong
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Transmitted to FAX Number:	484-344-2516
Attention:	Michael Elia, Ph.D.
Company Name:	Merck and Company, Inc.
Phone:	484-344-3180
Subject:	February 1, 2002 Meeting Minutes
Date:	February 15, 2002
Number of pages including this cover sheet:	4
From:	Sandy Birdsong
Phone:	301-594-5334
FAX:	301-594-5494

Dear Dr. Elia:

The minutes of our February 1, 2002 Teleconference accompanies this fax. You are responsible for notifying us of any differences in understanding you have of the meeting (as reflected in the minutes).
Thanks.

Sandy

Filing Summary and Meeting Minutes

NDA Number and Drug Name	NDA 20-386 COZAAR (losartan potassium)
Indication	Treatment of Type II Diabetic Nephropathy and the Reduction of Proteinuria
Sponsor	Merck and Company, Inc.
Therapeutic Classification	Therapeutic Antihypertensive
Date of Application	November 9, 2001
Date of Receipt	November 13. 2001
User Fee Goal	May 9, 2002 (6 month)
User Fee Status	Paid October 26, 2001 (ID# 4226)
Submission Complete As Required Under 21 CFR 314.50?	YES
Patent Information Included?	YES
Exclusivity Requested?	YES; 3 years
Debarment Statement Included?	YES
Pediatric Rule addressed?	Request for Full Pediatric Waiver Submitted
Financial Disclosure Information Included?	YES
Pre-NDA Meeting:	August 1, 2001 October 9, 2001

BACKGROUND

COZAAR was approved for the treatment of hypertension on April 14, 1995. An End of Phase II meeting was held March 8, 1996 during which the firm's proposed renal protection program and the primary RENAAL study was discussed. The original protocol for the RENAAL study was submitted to IND [redacted] on May 22, 1996.

A meeting was held with the firm on May 1, 2001 to discuss the preliminary results of the RENAAL trial. Dr. Temple agreed that Merck's request for Priority Review was consistent with the Agency's policy.
Pre-sNDA meetings occurred on August 1, 2001 and October 9, 2001 to discuss plans for submission of a supplemental NDA to support the use of COZAAR for treatment of type 2 diabetic patients with nephropathy and the reduction of proteinuria, as well as the structure and content of the supplemental NDA. A priority review was granted.

Dr. Lipicky noted that the *p*-value for the primary endpoint (p=0.022) was an order of magnitude higher than p<0.00125, the statistical significance that the Division prefers with a single study. However, he stated that the Division would not refuse to file. Assuming a November 2001 submission of the supplemental application, Dr. Lipicky said the application would probably be presented and discussed at the April 2001 Cardio-Renal Advisory Committee Meeting.

NDA supplement #028 was submitted as an electronic archive on November 9, 2001. After discussions between the Division and Merck statisticians, the sponsor submitted SAS datasets and descriptive documentation for the DSMB interim analysis on December 4, 2001.

Foreign Marketing History

As of October 1, 2001, COZAAR 100 mg Tablets are currently marketed in Canada, Mexico, Korea and Singapore, with applications pending in another 21 countries. COZAAR 50 mg Tablets have been approved in 94 countries.

Assigned Reviewers

Medical	Juan Carlos Pelayo, M.D.
Secondary Medical	Norman Stockbridge, Ph.D., M.D.
Pharmacology	Anthony Proakis, Ph.D.
Chemist	Ram Mittal, Ph.D.
Env. Assessment	N/A
Statistician	Jim Hung, Ph.D.
Biopharmaceuticist	Nhi Nguyen, Ph.D.
Microbiologist	N/A
DSI	Antoine El Hage, Ph.D.
Project Manager	Sandra Birdsong

Filing Meeting

Date: January 10, 2002

MEDICAL

One trial will be reviewed by Dr. Pelayo; Dr. Stockbridge will do the Secondary Medical Review. Dr. Stockbridge asked if irbesartan is approved, could it be changed to a Standard review. The PM determined that this could be done. Drs. Pelayo and Hung will do a combined Medical-Statistical review. Dr. Pelayo stated he will need approximately one week after he receives a *p*Value to complete his review, estimated to be the third week of March.

STATISTICAL

Dr. Hung is awaiting another data set from the sponsor, without which he cannot proceed. The project manager will contact the sponsor regarding the missing data set. Dr. Hung projected completion of his review for late March (by March 31, 2001).

BIOPHARMACEUTICS – On January 9, 2002 Dr. Marroum stated there were no biopharmaceutics issues.

PHARMACOLOGY

Dr. Proakis stated that [redacted]

Estimated completion date is March 15, 2002.

CHEMISTRY

On January 9, 2002 Dr. Srinivasachar stated there were no chemistry issues.

MICROBIOLOGY

N/A

DSI

Dr. Stockbridge believes that sites in China should be inspected because of the discrepancy in results with Western countries. The sites will be chosen and submitted to dr. El Hage. A request stating three sites for inspection, in priority order, the PDUFA date, Division Goal Date, review priority, and sponsor's contact information should be submitted to him.

Addendum: Drs. Throckmorton, Stockbridge and Pelayo met with the Project Manager present to choose two sites in China and one site in the U.S. This information was submitted to Dr. El Hage in a Request for Consultation with the other requested information on January 11, 2002.

REGULATORY REQUIREMENTS/ORGANIZATION –

The entire application was submitted electronically and is available to all reviewers in the electronic document room under NDA 20-386/SE1 028. Dr. Hung has had difficulty accessing additional information sent on December 20, 2001. Otherwise, the application appears to be well indexed and organized and appears suitable for filing.

Addendum: The Project Manager contacted the sponsor on January 11, 2002 regarding the December 20, 2001 submission. Dr. Michael Elia, Merck spoke with Dr. Levin regarding the electronic filing.

Sandra Birdsong, CSO

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/s/

Sandra Birdsong
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Minutes of a Meeting between Merck and the FDA

Date: October 9, 2001

Sponsor: Merck & Co., Inc.

Subject: NDA 20-386 Cozaar (Losartan Potassium) Tablets

Purpose: Pre-sNDA Meeting for Cozaar for the Treatment of Type 2 Diabetic Nephropathy and the Reduction of Proteinuria

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
Juan Carlos Pelayo, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Elizabeth Hausner, D.V.M., HFD-110, Pharmacologist
Edward Fromm, HFD-110, Project Manager

Merck

Michael Elia, Ph.D., Regulatory Affairs
Jeffrey Tucker, M.D., Regulatory Affairs
Shahnaz Shahinfar, M.D., Clinical Research
Roger Simpson, Clinical Research
Denise Ramjit, Clinical Research
Steven Snapinn, Ph.D., Biostatistics
Zhongxin Zhang, Ph.D., Biostatistics
Daniel Orfe, Electronic Regulatory Submissions
Betsy Fallen, Regulatory Coordination
Lauren Hetrick, Regulatory Agency Relations

Background

Cozaar (losartan potassium) was approved on April 14, 1995 for the treatment of hypertension. The firm requested a meeting to give an overview of their data from the RENAAL study that will be submitted in support of a new indication for Cozaar for the treatment of type 2 diabetic nephropathy and the reduction of proteinuria. Merck plans on submitting the supplemental NDA sometime in November 2001.

Meeting

Clinical Considerations

Dr. Lipicky opened the meeting by noting that the p-value for the RENAAL study was around 0.03, which is about an order of magnitude off the statistical significance usually required for a single study supporting a new drug or indication. Nevertheless, the application would not be refused to

file and since there is not a drug currently approved for the treatment of type 2 diabetic nephropathy, the supplement would be granted a priority review when submitted.

Merck said that in addition to the type 2 diabetic nephropathy claim, they were also seeking a claim for Cozaar for the reduction of proteinuria. They believe that data showing reduction of proteinuria complement the results for the RENAAL study. Dr. Lipicky replied that until more evidence comes in to the contrary, the Division will likely think of reduction of proteinuria as a surrogate endpoint. Merck said they would submit analyses to show that, even when corrections are made for blood pressure, a treatment effect for proteinuria reduction is still present.

Merck noted that Cozaar appears to have reduced protein in the urine in some patients by over 1 gm and asked if they could obtain a claim for Nephrotic Syndrome. Dr. Throckmorton said that Nephrotic Syndrome is defined by more than just a reduction of proteinuria; patients would have to be diagnosed with the condition (i.e., have signs and symptoms such as edema, hypercholesterolemia) before entering a study for the sponsor to use them as a basis for this claim.

Electronic Submission

Merck asked what datasets they should submit with their application. Dr. Lipicky said the following should be included in their submission:

- Case Report Forms (CRF's) with deaths and dropouts referenced
- Data Safety Monitoring Board (DSMB) minutes
- SAS datasets for any interim analyses plus final analysis
- SAS codes for all the analyses.

Dr. Lipicky noted that the firm's statistical plan appears to be acceptable.

Pediatrics

Dr. Throckmorton asked how the firm was planning to respond to the Pediatric Rule requirements for this indication. Merck replied that since the type 2 diabetic nephropathy was uncommon in children they would seek a pediatric waiver for this indication. Mr. Fromm reminded the firm to submit justification for this waiver request.

Advisory Committee

Merck asked if Cozaar for the treatment of type 2 diabetic nephropathy and reduction of proteinuria would be presented before a future Cardio-Renal Advisory Committee Meeting. Dr. Lipicky said it would probably be presented and if the firm submits their application in November the likely meeting date would be April of 2002.

Summary of Main Action Items

1. The firm will be granted a priority review (assuming submission in November 2001) for their supplement for Cozaar for the treatment of type 2 diabetic nephropathy and reduction of proteinuria.

2. The Division indicated that it will be difficult to obtain a claim of reduction of proteinuria because we believe that it is a surrogate endpoint.
3. The firm would have to have patients prospectively diagnosed with Nephrotic Syndrome before these patients could be used as basis for that claim.
4. If the submission arrives in November of this year, it will probably be presented at the April 2002 Cardio-Renal Advisory Committee Meeting.

Minutes Preparation: /S/
Edward Fromm

Concurrence: /S/
Raymond Lipicky, M.D.

dr/10-17-01/10-24-01

Rd: EHausner-10/23/01
JHung-10/23/01
JPelayo-10/23/01
NStockbridge-10/23/01
DThrockmorton-10/23/01

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/s/

Edward Fromm
10/25/01 03:33:12 PM
Dr. Lipicky signed the minutes on October 24, 2001.

FILING SUMMARY

NDA Number and Drug Name	NDA 20-386 COZAAR (losartan potassium)
Indication	Diabetic Nephropathy
Sponsor	Merck and Company, Inc.
Therapeutic Classification	Therapeutic Antihypertensive
Date of Application	November 9, 2001
Date of Receipt	November 13. 2001
User Fee Goal	May 9, 2002 (6 month)
User Fee Status	Paid October 26, 2001 (ID# 4226)
Submission Complete As Required Under 21 CFR 314.50?	YES
Patent Information Included?	YES
Exclusivity Requested?	YES; 3 years
Debarment Statement Included?	YES
Pediatric Rule addressed?	Request for Full Pediatric Waiver
Financial Disclosure Information Included?	YES
Pre-NDA Meeting:	August 1, 2001 October 9, 2001

BACKGROUND

COZAAR was approved for the treatment of hypertension on April 14, 1995. An End of Phase II meeting was held March 8, 1996 during which the firm's proposed renal protection program and the primary RENAAL study was discussed. The original protocol for the RENAAL study was submitted to IND [redacted] on May 22, 1996.

A meeting was held with the firm on May 1, 2001 to discuss the preliminary results of the RENAAL trial. Dr. Temple agreed that Merck's request for Priority Review was consistent with the Agency's policy. Pre-sNDA meetings occurred on August 1, 2001 and October 9, 2001 to discuss plans for submission of a supplemental NDA to support the use of COZAAR for treatment of type 2 diabetic patients with nephropathy and the reduction of proteinuria, as well as the structure and content of the supplemental NDA. A priority review was granted.

Dr. Lipicky noted that the p-value for the primary endpoint (p=0.022) was an order of magnitude higher than p<0.00125, the statistical significance that the Division prefers with a single study. However, he stated that the Division would not refuse to file. Assuming a November 2001 submission of the supplemental application, Dr. Lipicky said the application would probably be presented and discussed at the April 2001 Cardio-Renal Advisory Committee Meeting.

NDA supplement #028 was submitted as an electronic archive on November 9, 2001. After discussions between the Division and Merck statisticians, the sponsor submitted SAS datasets and descriptive documentation for the DSMB interim analysis on December 4, 2001.

Foreign Marketing History

As of October 1, 2001, COZAAR 100 mg Tablets are currently marketed in Canada, Mexico, Korea and Singapore, with applications pending in another 21 countries. COZAAR 50 mg Tablets have been approved in 94 countries.

Assigned Reviewers:

DISCIPLINE	REVIEWER
Medical	Juan Carlos Pelayo, M.D.
Secondary Medical	Norman Stockbridge, Ph.D., M.D.
Pharmacology	Anthony Proakis, Ph.D.
Chemist	Ram Mittal, Ph.D.
Env. Assessment	N/A
Statistician	Jim Hung, Ph.D.
Biopharmaceuticist	Nhi Nguyen, Ph.D.
Microbiologist	N/A
DSI	Earl Butler, Ph.D.
Project Manager	Sandra Birdsong

MEDICAL -

STATISTICAL -

BIOPHARMACEUTICS - N/A

PHARMACOLOGY -

CHEMISTRY -

Did firm request categorical exclusion for environmental assessment?

NO

EIR package transmitted? **NO**

Trade Name Review Requested? **NO**

MICROBIOLOGY - **N/A**

DSI –

REGULATORY REQUIREMENTS/ORGANIZATION –

The entire application was submitted electronically and is available to all reviewers in the electronic document room under NDA 20-386/SE1 028. The application appears to be well indexed and organized and appears suitable for filing.

/S/

Sandra Birdsong
Project Manager, HFD-110

Meeting Minutes
Regulatory Briefing

Date: April 1, 2002
Time: 3:30 – 5:00 p.m.
Location: WOC II, Conference Room C
Subject: NDA 20-386: Cozaar

Invitees/Attendees (Under Status, enter * if present)

Name	Status	Name	Status	Name	Status
Susan Allen	*	Chuck Anello	*	Jane Axelrad	
Rachel Behrman		Julie Beitz		Sandra Birdsong	*
Debra Birnkrant	*	Gary Buehler	*	Jonca Bull	*
Yuan Yuan Chiu		Kim Colangelo		Steven Galson	
Charles Ganley		Mark Goldberger		Debbie Henderson	
Maureen Hess		Martin Himmel		Chuck Hoiberg	
Florence Houn		Shiew-Mei Huang		Hsien Ming Hung	*
Ajaz Hussain		John Jenkins	*	Susan Johnson	
Rubynell Jordan		Russ Katz		Sandy Kweder	
John Lawrence	*	Larry Lesko	*	Ray Lipicky	
Patricia Love		Marianne Mann		Patrick Marroum	
Cynthia McCormick		Judy McIntyre	*	Robert Meyer	
Natalia Morgenstern		Diane Murphy		Bob O'Neill	
David Orloff		Michael Ortwerth	*	Bob Osterberg	
Lana Pauls		Richard Pazdur	*	Juan Carlos Pelayo	*
Victor Raczkowski		Paul Seligman	*	Nancy Smith	
Sol Sobel	*	Janice Soreth		Norman Stockbridge	*
Bob Temple	*	Doug Throckmorton	*	Robert West	
Jonathan Wilkin		Helen Winkle		Janet Woodcock	*
Denise Hinton	*	Lee Ripper	*	Dave Roeder	*

Agenda

Time	Item #	Agenda Item	Presenter
5 min.	1	Opening Remarks	John Jenkins
15 min.	2	Division Presentation	Doug Throckmorton
15 min.	3	Office Presentation	Bob Temple
40 min.	4	Opinions/Discussion	Panel and Division
15 min.	5	Wrap Up	John Jenkins

Minutes

Agenda Item No.	Main Points, Decisions, Next Steps
1	Dr. John Jenkins, Director, Office of New Drugs, opened the meeting with brief remarks about the topic of the meeting and introduced the speakers.

Agenda Item No.	Main Points, Decisions, Next Steps
2	Dr. Doug Throckmorton presented background information about the topic. Two trials of drugs with similar pharmacological activity (irbesartan and losartan, both Angiotensin II Receptor Blockers, ARBs) have recently been submitted to the Agency in support of claims for the treatment of patients with diabetes and nephropathy. Irbesartan (the IDNT trial) was presented to the Advisory Committee meeting in January and resulted in a split vote against approval. Following the Advisory Committee, the supplement for irbesartan was withdrawn. Losartan has now submitted their data from the RENAAL study in patients with type 2 diabetes and nephropathy to the FDA. This data will be presented to the Advisory Committee on April 12, 2002. The sponsors for irbesartan and losartan have submitted letters of 'right to reference' to allow their respective trials (RENAAL and IDNT) to be considered by the committee as potentially supportive of efficacy for both irbesartan and losartan, and for the FDA to consider the data from both trials in support of their respective claims. Neither study alone has the strength that would ordinarily be expected when the Agency relies on a single study for approval. Dr. Throckmorton also reviewed an example of the Agency apparently relying on clinical trials in pharmacologically related drugs to support efficacy (ACE-Inhibitors and CHF). In that case the new study supporting each ACE I was not alone statistically robust (P between 0.05 and 0.01); there were, however, a number of studies showing a benefit from various ACEI's in similar populations. See Attachment 1 for more details. The Division requests comment from the panel and audience about their experience and views on the use of efficacy data from related drugs. In this case clear permission has been granted by the respective sponsors to do so.
3	Dr. Temple provided information from the Guidance document on Clinical Evidence as well as examples and preliminary thoughts on the implications for the present case. See Attachment 2 for the slides from his presentation.
4	General discussion: • Prior to the Advisory Committee for irbesartan, the Division had not taken a formal position, but believed the IDNT trial borderline to support approval. The primary medical reviewer, Dr. Pelayo, recommended approval for both the irbesartan and losartan supplements. After the Advisory Committee recommendation, if the sponsor had not withdrawn the supplement, the Division was prepared to issue a not approveable letter citing the need for additional clinical data. Following the withdrawal of the supplement, no Withdrawal Acknowledgement letter listing the deficiencies was sent to the sponsor. • The Advisory Committee had two nephrologists invited as voting members for the two applications. It was suggested that future Advisory Committee should have more nephrologists on the panel when issues related directly to their area of expertise are to be discussed. • If approved, the label for losartan will not refer to irbesartan (and vice-versa). In cases where this type of action was done implicitly, the label does not refer to the other product (e.g., drugs used for the treatment of osteoporosis).